ARYL-ETHANOLAMINE DERIVATIVES AS ANTIVIRAL AGENTS

CROSS REFERENCE

This application claims the benefit of the following provisional application: US Serial No 60/408,206, filed 9/4/2002 under 35 USC 119(e)(i), which is incorporated herein by reference in its entirety

FIELD OF THE INVENTION

The present invention discloses aryl-ethanolamine derivatives, and more specifically, provides compounds of formula (I) described herein below. These compounds are useful as antiviral agents, in particular, as agents against viruses of the herpes family.

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. They are also a source of the most common viral illnesses in man. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans.

HSV-1 and HSV-2 cause herpetic lesions on the lips and genitals, respectively. They also occasionally cause infections of the eye and encephalitis. HCMV causes birth defects in infants and a variety of diseases in immunocompromised patients such as retinitis, pneumonia, and gastrointestinal disease. VZV is the causitive agent of chicken pox and shingles. EBV causes infectious mononucleosis. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease. HHV-6 is the causative agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in some cases of roseola. HHV-8 has been associated with Karposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

Infection by or reactivation of herpesviruses is associated with several cardiovascular diseases or conditions in the host such as atherosclerosis and restenosis resulting in inflammation of coronary vessel walls. It is thought that in many patients suffering from restenosis following coronary atherectomy viral infection particularly by CMV plays an important role in the proliferation of the disease. Atherosclerosis is believed to be associated with the overall infectious disease burden in the host and particularly by the herpesviruses such as HSV, CMV, and EBV.

Infection in the animal population (livestock and companion) by strains of herpesviruses is endemic including cattle (Bovine herspesvirus 1-5, BHV), sheep (Ovine herpesvirus 1 and 2), dog (Canine herpesvirus 1), horse (Equine herpesvirus 1-8, EHV), cat (Feline herpesvirus 1, FHV), swine (pseudorabies virus, PRV), and many species of fowl. In the case of bovine herpesvirus infection, animals may suffer from ocular, respiratory, or digestive disorders. Pseudorabies is an extremely contagious viral pathogen infecting several species such as cattle, horses, dogs, cats, sheep, and goats leading to rapid death. The virus is benign in adult swine, however, it remains contagious and leads to high mortality in pigs under three weeks. Infection of horses by equine herpesvirus may lead to neurological syndromes, respiratory disease, and neonatal disease. Herpesvirus infection in cats leads to the disease known as feline viral rhinotracheitis (FVR) which is characterized by rhinitis, tracheitis, laryngitis, and conjunctivitis.

Due to the unique position of the aryl substitutent on the formula I described herein below, compounds of the present invention demonstrate unexpected activity against the above reference herpesviral infections, particularly, human cytomegaloviral infection.

INFORMATION DISCLOSURE

US 6,239,142 disclosed compounds and their use to treat herpesvirus infections.

WO02/06513 disclosed method of screening 4-hydroxyquinline, 4-oxo-dihydroquinoline, and 4-oxo-dihydrothienopyridine derivatives as non-nucleoside herpesvirus DNA polymerase inhibitors.

Tetrahedron Lett. 1983, *24*, 3233-3236 describes conditions to transform tertiary *N*-benzylamines into benzylchlorides.

WO95/28405 disclosed bicyclic thiophene derivatives and use as gonadotropin releasing hormone Antagonists).

EP 443568 disclosed fused thiophene derivatives, their production and use.

WO02/04445 disclosed a variety of tricyclic core structures which have antiviral activity against herpesviruses.

WO02/04444, WO02/04443, and WO02/04422 disclosed a variety of bicyclic core structures which have antiviral activity against herpesviruses.

US 6,248,739 disclosed compounds in which the core structure is a quinoline and useful as antivirals against herpesviruses.

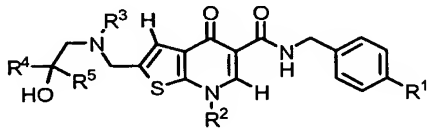
WO00/53178, WO00/53179, WO00/53180, WO00/53181, WO00/53185, and WO00/53602 disclosed 6-azaindole compounds as antagonists of gonadotropin releasing hormone.

US 6,346,534 and WO00/69859 disclosed imidazo- and pyrrolo[1,2-*a*]pyrimid-4-ones as gonadotropin-releasing hormone receptor antagonists.

WO 94/12461 disclosed a variety of bicyclic core structures useful as potential treatments of AIDS, asthma, arthritis, and other inflammatory diseases.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



I

its enantiomeric, diasteromeric or tautomeric isomer, or a pharmaceutically acceptable salt thereof wherein,

R^1 is

(a) Cl,

(b) Br,

(c) F, or

(d) CN;

R^2 is

(a) $C_{1\text{-}4}$alkyl optionally substituted by one or more OH or $C_{1\text{-}4}$alkoxy, or

(b) $(CH_2)_mOCH_2CH_2OH$;

R^3 is C_{1-2}alkyl;

R^4 is a aryl, wherein aryl is phenyl, optionally fused to a benzene or pyridine ring, and optionally substituted with one or more R^6;

R^5 is

(a) H, or

(b) C_{1-2}alkyl optionally substituted by OH;

R^6 is

(a) halo,

(b) OCF_3,

(c) cyano,

(d) nitro,

(e) $CONR^7R^8$,

(f) NR^7R^8,

(g) C_{1-7}alkyl, which is optionally partially unsaturated and is optionally substituted by one or more R^9,

(h) $O(CH_2CH_2O)_nR^{10}$,

(i) OR^{10},

(j) CO_2R^{10},

(k) phenyl optionally substituted by halo, C_{1-7}alkyl, or C_{1-7}alkoxy;

(l) SR^{10},

(m) imidazolyl,

(n) $S(O)_mNR^7R^8$,

(o) $NHC(=O)R^{10}$, or

(p) Any two adjacent R^6 substituents taken together constitute a group of the formula $-O(CH_2)_mO-$, $-(NH)(CO)(CH_2)_jO-$, or $-(CH_2)_i-$;

R^7 and R^8 are independently

(a) H,

(b) phenyl optionally substituted by halo, C_{1-7}alkyl, or C_{1-7}alkoxy,

(c) C_{1-7}alkyl which is optionally substituted by one or more OR^{10}, phenyl, or halo substituents,

(d) C_{3-8}cycloalkyl,

(e) $(C=O)R^{11}$, or

(f) R^7 and R^8 together with the nitrogen to which they are attached form a het, wherein het is a five- (5), or six- (6) membered heterocyclic ring having one (1), two (2), or three (3) heteroatoms selected from the group consisting of oxygen, sulfur, or nitrogen, wherein het is optionally substituted with C_{1-4} alkyl;

R^9 is

(a) oxo,

(b) phenyl optionally substituted by halo, C_{1-7}alkyl, or C_{1-7}alkoxy,

(c) OR^{10},

(d) $O(CH_2CH_2)OR^{10}$,

(e) SR^{10},

(f) NR^7R^8,

(g) halo,

(h) CO_2R^{10},

(i) $CONR^{10}R^{10}$, or

(j) C_{3-8}cycloalkyl optionally substituted by OR^{10};

R^{10} is

(a) H,

(b) C_{1-7}alkyl,

(c) C_{3-8}cycloalkyl, or

(d) phenyl optionally substituted by halo, C_{1-7}alkyl, or C_{1-7}alkoxy;

R^{11} is

(a) C_{1-7}alkyl,

(b) C_{3-8}cycloalkyl, or

(c) phenyl optionally substituted by halo, C_{1-7}alkyl, or C_{1-7}alkoxy;

i is 3 or 4;

j is 0 or 1;

n is 1, 2, 3, 4 or 5; and

each m is independently 1 or 2.

In another aspect, the present invention also provides:

A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I,

a method of treating and preventing herpesviral infections in a mammal comprising administering to a mammal in need thereof a compound of formula I, or a pharmaceutically acceptable salt thereof,

a method for inhibiting a viral DNA polymerase comprising contacting, in vivo or in vitro, the polymerase with an effective inhibitory amount of a compound of formula I, or a pharmaceutically acceptable salt thereof,

a compound of formula I or a pharmaceutically acceptable salt thereof for use in medical treatment or prevention of a herpesviral infection in a mammal.

The invention also provides novel intermediates and processes disclosed herein that are useful for preparing compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C_{1-7})alkyl refers to alkyl of one to seven carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, pentyl, hexyl, and heptyl, straight and branched forms thereof.

The term "halo" or "halogen" refers to the elements fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

The term "C_{3-8}cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms.

The term "alkoxy" refers to the group RO-, wherein R is alkyl or cycloalkyl as defined above.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral

stationary phase) and how to determine antiviral activity using the standard tests described herein, or using other similar tests which are well known in the art.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system.

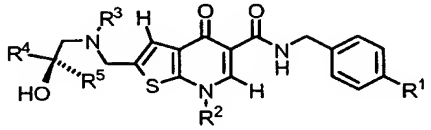
"Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable.

"Mammal" refers to human and animals. Animals specifically refer to, for example, food animals or companion animals.

"Optionally" or "may be" means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

A "pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

Specifically, formula I of the present invention has a stereogenic center as shown in formula IA:



IA.

Specifically, a composition comprising over 51% of a compound of formula IA.

Specifically, a composition comprising over 75% of a compound of formula IA.

Specifically, a composition comprising over 90% of a compound of formula IA.

Specifically, a composition comprising over 98% of a compound of formula IA.

Specifically, R^1 is chloro.

Specifically, R^2 is C_{1-3}alkyl.

Specifically, R^2 is methyl, ethyl, or *n*-propyl.

Specifically, R^2 is methyl.

Specifically, R^2 is C_{1-3}alkyl substituted with one or two hydroxy.

Specifically, R^2 is 2-hydroxyethyl, 3-hydroxypropyl, or 2,3-dihydroxypropyl.

Specifically, R^2 is C_{1-4}alkyl substituted by C_{1-4}alkoxy.

Specifically, R^2 is C_{1-4}alkyl substituted by methoxy.

Specifically, R^2 is 2-methoxyethyl.

Specifically, R^3 is methyl.

Specifically, R^3 is ethyl.

Specifically, R^4 is phenyl, optionally substituted with one or more R^6.

Specifically, R^4 is phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-bromophenyl, 4-bromophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-hydroxyphenyl, 3, hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 3-phenoxyphenyl, 3-(4-chlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(4-methylphenoxy)phenyl, 3,4-dibromophenyl, 2-chloro-5-trifluoromethylphenyl, 3,5-dibromophenyl, 3,5-dibromo-6-methoxyphenyl, 3,5-di(trifluoromethyl)phenyl, 3-cyano-4-fluorophenyl, 3-bromo-4-fluorophenyl, 2-bromophenyl, 3-bromo-6-fluorophenyl, 4-bromo-6-fluorophenyl, 3-bromo-6-hydroxyphenyl, 3-bromo-4-methoxyphenyl, 4-(1*H*-imidazol-1-yl)phenyl, 3, bromo-6-methoxyphenyl, 4-nitrophenyl, 4-chloro-5-fluorophenyl, 2-chloro-6-fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 4-hydroxy-5-methoxyphenyl, 4-(acetylamino)phenyl, 3-(acetylamino)phenyl, 4-hydroxy-5-methylphenyl, 2-thiomethylphenyl, 3-fluoro-2-methylphenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 4-hydroxymethylphenyl, 3-hydroxymethylphenyl, 2-hydroxymethylphenyl, 4-aminophenyl, 3-aminophenyl, 2-fluoro-4-trifluoromethylphenyl, 2-methyl-4-methoxyphenyl, 4-dimethylaminophenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-hydroxy-5-methoxyphenyl, 4-(2-hydroxyethoxy)phenyl, 4-morpholin-4-ylphenyl, 1,1'-

biphenyl-4-yl, 1,1'-biphenyl-3-yl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,6-difluorophenyl, 2,5-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2,3,6-trifluorophenyl, 2,3,5-trifluorophenyl, or 2,3,4,5,6-pentafluorophenyl.

Specifically, R^4 is 2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl, 3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, 1,3-benzodioxol-4-yl, 6-chloro-1,3-benzodioxol-5-yl, or 7-methoxy-1,3-benzodioxol-5-yl.

Specifically, R^4 is phenyl, 4-hydroxyphenyl, 3-methoxyphenyl, 4-cyanophenyl, or 3-cyanophenyl.

Specifically, R^4 is naphthyl, optionally substituted with one or more R^6.

Specifically, R^4 is 2-naphthyl or 1-naphthyl.

Specifically, R^4 is 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 4-dimethylamino-1-naphthyl, 4-methyl-1-naphthyl, 4-hydroxy-1-naphthyl, or 6-methoxy-2-naphthyl.

Specifically, R^4 is phenyl fused to a pyridine ring, optionally substituted with one or more R^6.

Specifically, R^4 is quinolin-8-yl, isoquinolin-8-yl, isoquinolin-5-yl, quinolin-5-yl, quinolin-7-yl, isoquinolin-7-yl, isoquinolin-6-yl, or quinolin-6-yl.

Specifically, R^5 is hydrogen.

Specifically, R^5 is methyl or ethyl.

Specifically, R^5 is hydroxymethyl, 1-hydroxyethyl, or 2-hydroxyethyl.

Specifically, R^6 is OH, halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, nitro, OCF_3, NR^7R^8, phenyl, or $CONR^7R^8$.

Specifically, R^6 is OH, methoxy, or cyano.

Examples of the present invention include, but are not limited to the following:

(1) *N*-(4-chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-hydroxyphenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(2) *N*-(4-chlorobenzyl)-2-((((2S)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(3) *N*-(4-Chlorobenzyl)-7-(2,3-dihydroxypropyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(4) *N*-(4-chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(5) *N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)-(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(6) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(3-methoxyphenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(7) *N*-(4-Chlorobenzyl)-7-ethyl-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)-amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(8) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-7-propyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(9) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(10) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-cyanophenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(11) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(3-cyanophenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(12) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-(4-(dimethylamino)phenyl)-2-hydroxyethyl)-(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(13) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-(hydroxymethyl)phenyl)ethyl)-(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,.

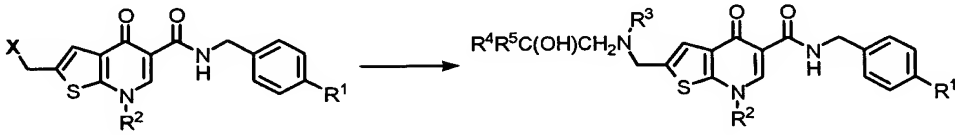
(14) *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-nitrophenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide. and pharmaceutically acceptable salts thereof.

Charts A-M describe the preparation of the compounds of Formula (I) of the present invention. All of the starting materials are prepared by procedures described in these charts, by procedures well known to one of ordinary skill in organic chemistry or can be obtained commercially. All of the final compounds of the present invention are prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry.

Compounds of Formula (I) are prepared as described in Chart A. Compounds of the formula A.1 in which X is a leaving group (e.g. mesylate, chloride, or bromide)

are treated with a secondary amine of the formula $R^4R^5C(OH)CH_2NH(R^3)$ in the presence of a non-nucleophilic base (e.g. diisopropylethylamine) in a polar solvent (e.g. DMF) to afford products of the formula A.2. It would be understood by those skilled in the art that in some cases transient protection of hydroxyl and other Lewis basic or acidic functionality present in $R^4R^5C(OH)CH_2NH(R^3)$ may be required to facilitate the coupling described in Chart A for which procedures are well established (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 1999).

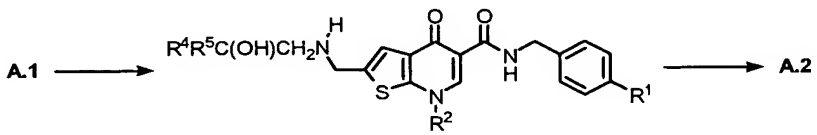
CHART A



A.1 A.2

Alternatively, compounds of Formula (I) are prepared as described in Chart B. Compounds of the formula A.1 in which X is a leaving group (e.g. mesylate, chloride, or bromide) are treated with a primary amine of the formula $R^4R^5C(OH)CH_2NH_2$ in the presence of a non-nucleophilic base (e.g. diisopropylethylamine) in a polar solvent (e.g. DMF) to afford products of the formula B.1. The resulting secondary amine is then alkylated by reactions generally known by those skilled in the art such as (1) the reaction of B.1 with a corresponding alkylhalide, dialkylsulfonate, or alkylarylsulfonate or (2) the reaction of B.1 with an aldehyde (e.g. formaldehyde or acetaldehyde) in the presence of a reducing agent (e.g. sodium cyanoborohydride or sodium triacetoxyborohydride) to afford compounds of the general formula A.2.

CHART B

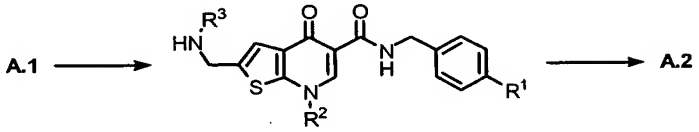


B.1

Alternatively, compounds of Formula (I) are prepared as described in Chart C. Compounds of the formula A.1 in which X is a leaving group (e.g. mesylate, chloride,

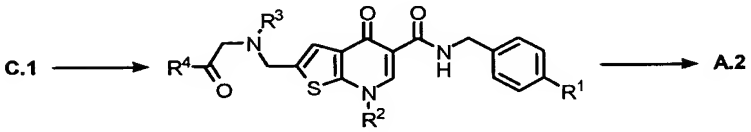
or bromide) are treated with an alkyl primary amine (e.g. methylamine or ethylamine) in the presence of a non-nucleophilic base (e.g. diisopropylethylamine) in a polar solvent (e.g. DMF) to afford products of the formula C.1. The resulting secondary amine is then treated with an electrophile either of the formula $R^4R^5C(OH)CH_2X$ (where X is Cl, Br) in the presence of a non-nucleophilic base (e.g. diisopropylethylamine) in a polar solvent (e.g. DMF) or with an epoxide to afford products of the formula A.2. Alternatively, compounds of the formula C.1 are alkylated with 2-haloketones of the formula $R^4C(O)CH_2X$ (where X is Cl, Br) according to Chart D to afford products of the formula D.1. The resulting amino ketones are then reduced with an appropriate achiral or chirally-modified reducing agent (e.g. $NaBH_4$ or diisopinocamphenylchloroborane) to provide compounds of the formula A.2.

CHART C



C.1

CHART D



D.1

The precursors A.1 are available from the corresponding alcohols (Y = OH) by treatment with methanesulfonyl chloride in the presence of an organic base (e.g. pyridine or 2,4,6-collidine) and if needed an activating agent (e.g. DMAP), Chart E. Alternatively, compounds of the formula A.1 are available by treatment of a tertiary amino derivative (e.g. Y = $N(CH_3)_2$ or 4-morpholinyl) with ethyl chloroformate in an appropriate solvent (e.g. chloroform).

CHART E

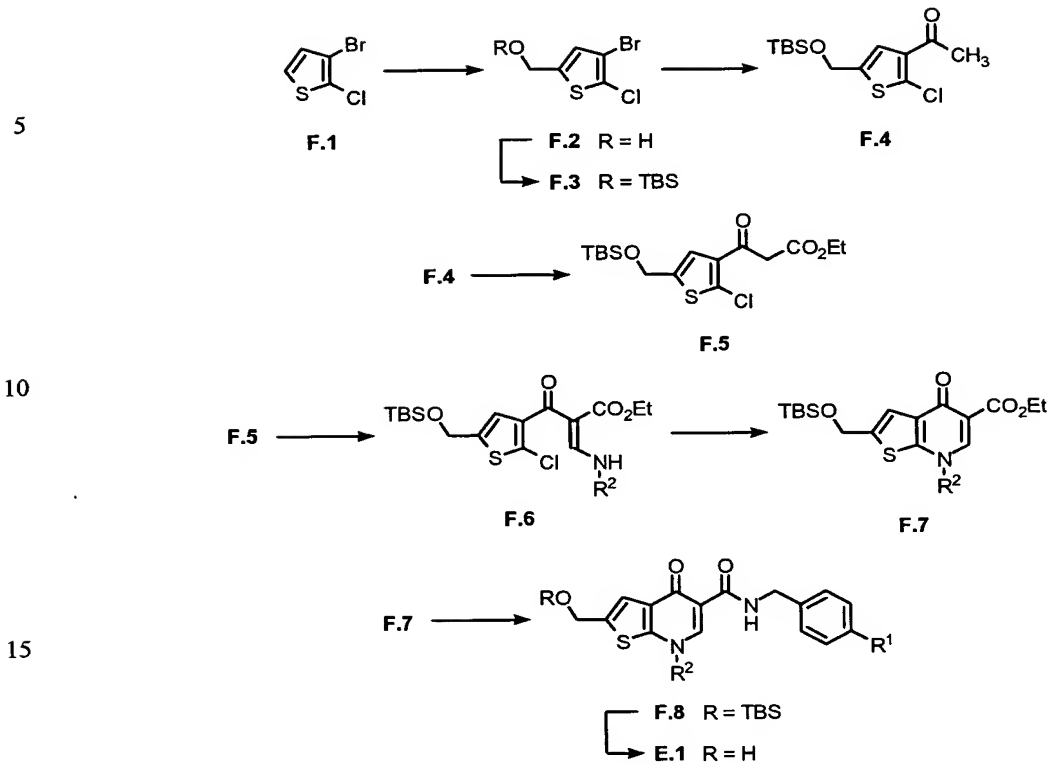
E.1
Y = OH, NR_2

A.1
X = OMs, Cl

Subsequently, compounds of the general formula E.1 are prepared according to procedures described in US patent 6,239,142 or exemplified in Charts F, G, and H below.

As described in Chart F, 3-bromo-2-chlorothiophene (F.1) is metalated with lithium diisopropyl amide in tetrahydrofuran at low temperature followed by addition to paraformaldehyde to provide alcohol F.2. The free hydroxyl is protected employing common methodology (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 1999) such as the tert-butyldimethylsilyl ether (TBS) by treatment with the corresponding silyl chloride and a weak base (e.g. imidazole) in a polar solvent (e.g. DMF). Metalation of F.3 with *n*-butyl lithium followed by addition to *N*-methoxy-*N*-methylacetamide provides the methyl ketone F.4. Condensation of F.4 with diethyl carbonate in the presence of a strong base (e.g. sodium hydride) affords ketoester F.5. Compound F.5 is then refluxed in a mixture of acetic anhydride and triethylortho-formate to afford an intermediate enol ether which is then condensed with a primary amine or aniline (e.g. R^2NH_2) to provide a compound of the formula F.6. The resulting enamines are cyclized by heating in the presence of a base (e.g. sodium hydride, potassium carbonate, or potassium *tert*-butoxide) in an appropriate solvent (e.g. THF, DMF, or *tert*-butanol) to provide F.7. Esters of the formula F.7 are converted to amides of the general formula F.8 by either (a) treatment with a substituted benzylamine (e.g. 4-chlorobenzylamine, 4-fluorobenzylamine, or 4-bromobenzylamine) at high temperature or (b) saponification by treatment with an inorganic base such as sodium hydroxide to afford the corresponding carboxylic acid which is then coupled with a substituted benzylamine mediated by 1,1′-carbonyl-diimidazole (or other suitable carboxylic acid activating agent). Subsequent deprotection of the hydroxyl protecting group to afford E.1 is accomplished through common procedures such as treatment with tetrabutylammonium fluoride in the case of silyl ether protection.

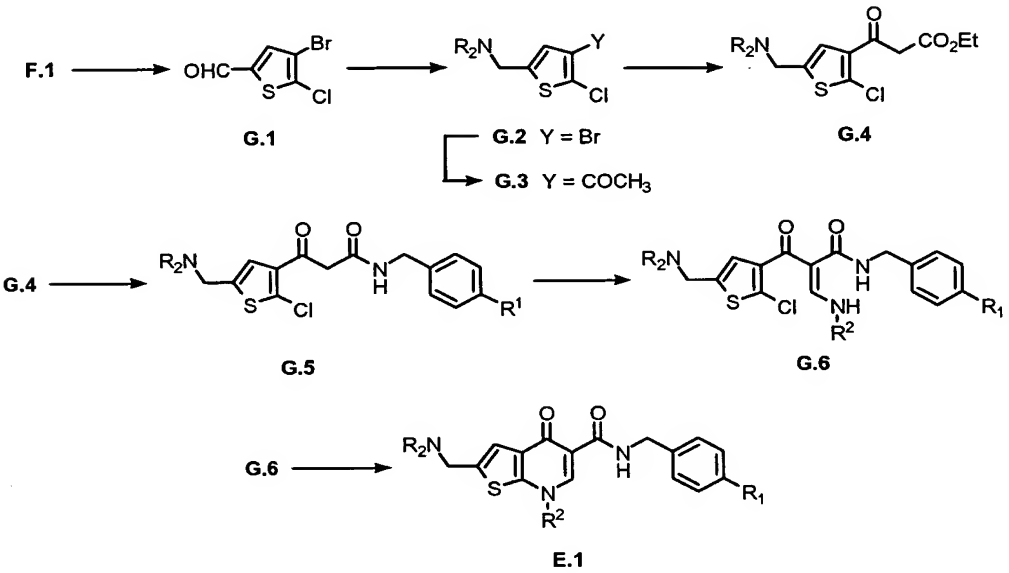
CHART F



Compounds of formula E.1 (Y = NR_2) may be prepared as described in Chart G. 3-Bromo-2-chlorothiophene (F.1) is metalated with lithium diisopropyl amide in tetrahydrofuran at low temperature and condensed with *N*,*N*-dimethylformamide to afford the carboxaldehyde G.1. Reductive amination of G.1 by treating with an amine (e.g. morpholine), acetic acid, and an appropriate reducing agent (e.g. sodium triacetoxyborohydride) affords thiophenes of the formula G.2. Metalation of G.2 with *n*-butyl lithium followed by addition to *N*-methoxy-*N*-methylacetamide provides the methyl ketone G.3. Condensation of G.3 with diethyl carbonate in the presence of a strong base (e.g. sodium hydride) affords ketoester G.4. The resulting ketoester is then treated with a benzylamine (e.g. 4-chlorobenzylamine, 4-fluorobenzylamine, or 4-bromobenzylamine) in refluxing xylene to provide ketoamides of the formula G.5. Compound G.5 is then refluxed in a mixture of acetic anhydride and triethylorthoformate to afford an intermediate enol ether which is then condensed with a primary amine or aniline (e.g. R^2NH_2) to provide a compound of the formula G.6. The resulting enamines are cyclized by heating in the presence of a base (e.g. sodium

hydride, potassium carbonate, or potassium *tert*-butoxide) in an appropriate solvent (e.g. THF, DMF, or *tert*-butanol).

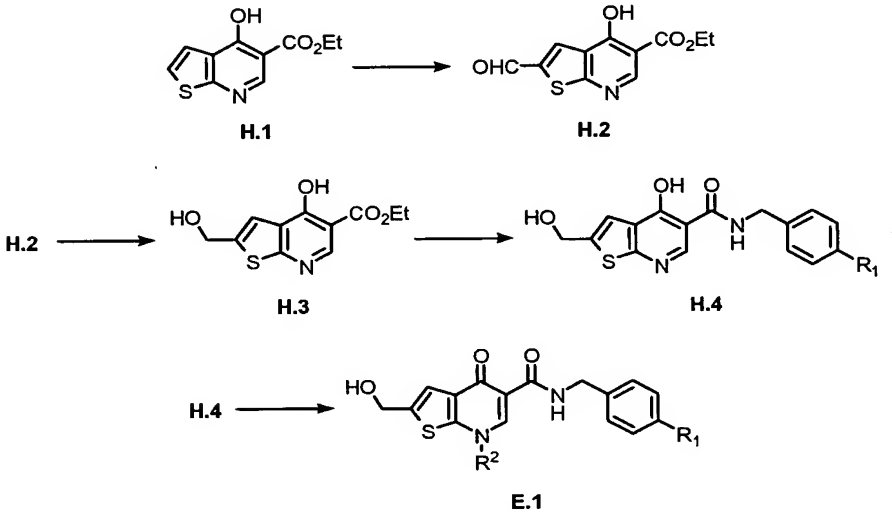
CHART G



Alternatively, compounds of formula E.1 (Y = OH) may be prepared as described in Chart H. Ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate (*J. Heterocyclic Chem.* **1977**, *14*, 807) is metallated with from two to six equivalents of lithium diisopropylamide at low temperature and is then reacted with dimethylformamide to provide compound H.2. Treatment of H.2 with an appropriate reducing agent (e.g. $NaBH_4$) in a polar solvent (e.g. ethanol) affords the alcohol H.3. The resulting ester is then reacted with a substituted benzylamine (e.g. 4-chlorobenzylamine, 4-fluorobenzylamine, or 4-bromobenzylamine) at high temperature or under other common amide forming conditions well known to those skilled in the art to provide compounds of the formula H.4. Compound H.4 is alkylated at the ring nitrogen by treatment with an optionally substituted alkyl halide or alkyl sulfonate ester in the presence of a base (e.g. potassium carbonate) or by reaction with an optionally substituted alkanol under Mitsunobu conditions to afford compounds of the general formula E.1. Specific examples of such alkyl halides used in this reaction include but are not limited to iodomethane, iodoethane, 1-iodopropane, 1-iodobutane, and 1-bromo-2-methoxyethane. It would be understood by those skilled in the art that in some cases transient protection of hydroxyl functionality present in the R^2X (X = halo

or sulfonate) or R^2OH reagent used in the above step may be required to facilitate the coupling described in Chart H or subsequent chemistry described in Charts A – E. Specific examples of such protected-hydroxyalkyl halides used in this reaction include but are not limited to 2-(2-bromoethoxy)tetrahydro-2*H*-pyran, 2-(3-bromopropoxy)tetrahydro-2*H*-pyran, 2-(3-iodopropoxy)tetrahydro-2*H*-pyran, 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane, 2-(2-chloroethoxy)ethoxy)tetrahydro-2*H*-pyran, 2-(2-iodoethoxy)tetrahydro-2*H*-pyran, and 2-(chloromethoxy)ethyl benzoate. Procedures to deprotect these cases at the final or intermediate stage are well established (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 1999).

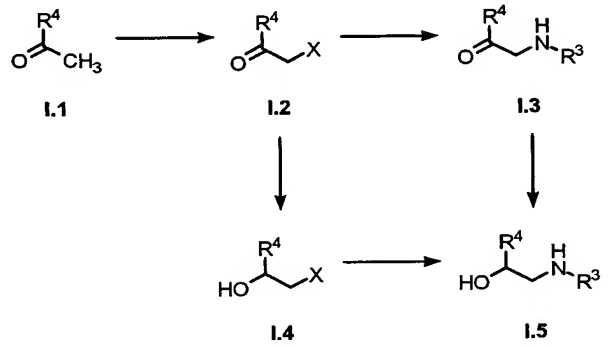
CHART H



The amine $R^4R^5C(OH)CH_2NH(R^3)$ in Chart A may be commercially available, can be prepared by procedures know to those skilled in the art, or can be prepared by methods illustrated in Charts I - M. As shown in Chart I, commercially available methylketones I.1 can be halogenated (X = Cl, Br) to provide the haloketones of the formula I.2. The resulting haloketones can be reduced to yield the corresponding halohydrins I.3 employing either achiral (e.g. $NaBH_4/CeCl_3$) or chiral reduction conditions. The resulting halohydrin is then treated with a primary amine (e.g. methylamine or ethylamine) to afford amins of the formula I.5. Alternatively, the haloketones can be treated directly with the primary amine (e.g. methylamine or ethylamine) to provide an aminoketone I.4 which can then be reduced under achiral or

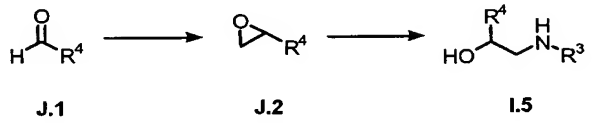
chiral reduction conditions to afford compounds of the formula I.5. In this case, the basic nitrogen may require transient protection (e.g. *tert*-butylcarbamate) to facilitate the reduction.

CHART I



Alternatively, as shown in Chart J specific amines of the formula $R^4R^5C(OH)CH_2NH(R^3)$ can be prepared from carboxaldehydes J.1 which are commercially available or prepared by methods known to those skilled in the art. Epoxidation of J.1 with a sulfonium ylide (e.g. trimethylsulfonium iodide) affords epoxides of the formula J.2. Treatment of the epoxides with a primary amine (e.g. methylamine or ethylamine) provides compounds of the formula I.5.

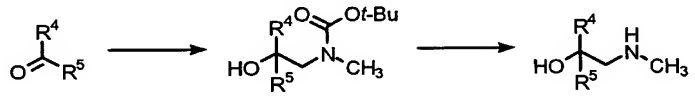
CHART J



As shown in Chart K, specific amines of the formula $R^4R^5C(OH)CH_2NH(R^3)$ are also prepared from carbonyl derivatives K.1 by the reaction with metalated *tert*-butyl dimethylcarbamate in the presence of tetramethylenediamine at low temperature to afford the BOC-protected amino alcohol K.2. Subsequent cleavage under acidic conditions (e.g. trifluoroacetic acid or hydrochloric acid) or oxazolidinone cyclization under basic conditions (e.g. sodium hydride) followed by basic hydrolysis provides compounds of the formula K.3. In cases where R^5 is hydroxymethyl, 2-hydroxyethyl, or 1-hydroxyethyl, the hydroxyl group is transiently protected using common

protecting groups (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 1999) and then deprotected either prior to or after coupling as described in Chart A.

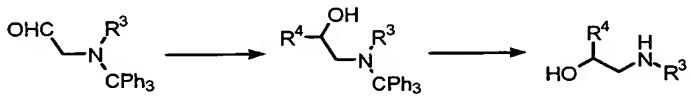
CHART K



K.1 K.2 K.3

As shown in Chart L, specific amines of the formula $R^4R^5C(OH)CH_2NH(R^3)$ are also prepared from a protected form of methylaminoacetaldehyde or methylamino-acetaldehyde (e.g. (methyl(trityl)amino)acetaldehyde) (L.1). Treatment of L.1 with a metalated heteroaryl reagent at low temperature affords alcohols of the formula L.2. Subsequent deprotection of the nitrogen protecting group (e.g. in the case of trityl, treatment with an inorganic acid in etheral solution) provides amines of the formula I.5. It would be understood by those skilled in the art that in some cases transient protection of Lewis basic or acidic functionality present in the R^4 substituent may be required to facilitate the metal reagent formation and subsequent addition described in Chart L for which procedures are well established (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 1999).

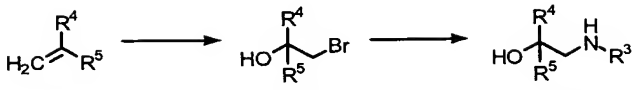
CHART L



L.1 L.2 I.5

In cases where the R^5 substituent of the amine $R^4R^5C(OH)CH_2NH(R^3)$ is methyl or ethyl, the amine may be prepared as described in Chart M. The olefin M.1 is reacted with *N*-bromosuccinamide in an ether solvent employing a catalytic amount sulfuric acid to afford the bromohydrin M.2. The resulting bromohydrin is then treated with a primary amine (e.g. methylamine or ethylamine) to afford amines of the formula M.3.

CHART M



M.1 M.2 M.3

Methods to prepare primary amines of the formula $R^4R^5C(OH)CH_2NH_2$ for use in Chart B are well known to those skilled in the art of organic synthesis (Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561-2576; Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.).

The compounds of Formula (I) may be prepared as single enantiomer or as a mixture of individual enantiomers which includes racemic mixtures. Methods to obtain preferentially a single enantiomer from a mixture of individual enantiomers or a racemic mixture are well known to those ordinarily skilled in the art of organic chemistry. Such methods include but are not limited to preferential crystallization of diastereomeric salts (e.g. tartrate or camphor sulfonate), covalent derivatization by a chiral, non-racemic reagent followed by separation of the resulting diastereomers by common methods (e.g. crystallization, chromatographic separation, or distillation) and chemical reversion to scalemic compound, Simulated Moving Bed technology, or high/medium-pressure liquid chromatography employing a chiral stationary phase (Eliel, E. L. *Stereochemistry of Organic Compounds*, 1994; Subramanian, G. *Chiral Separation Techniques: A Practical Approach*, 2001). These techniques may be performed on the final compounds of Formula (I) or on any intermediates to compounds of Formula (I) which bear a sterogenic center. Also, to facilitate separation by any of the methods described above, the compounds of Formula (I) or any intermediates to the compounds of Formula (I) which bear a stereogenic center may be transiently reacted with an achiral reagent, seperated, and then reverted to scalemic compound by standard synthetic techniques.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and alternative synthetic processes are known to one of ordinary skill in organic chemistry.

The compounds of the present invention and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, these compounds are useful to combat viral

infections in mammals. Specifically, these compounds have anti-viral activity against the herpes virus, cytomegalovirus (CMV). These compounds are also active against other herpes viruses, such as the varicella zoster virus, the Epstein-Barr virus, the herpes simplex virus, and the human herpes virus type 8 (HHV-8).

The compounds of the present invention may also be useful for the treatment of several cardiovascular diseases such as atherosclerosis and restenosis. These diseases have been implicated with inflammation of coronary vessel walls resulting from infection or reactivation of herpesviruses.

The compounds of the present invention may also be useful for the treatment of herpesvirus infections in animals, for example, illnesses caused by bovine herpesvirus 1-5 (BHV), ovine herpesvirus 1 and 2, Canine herpesvirus 1, equine herpesvirus 1-8 (EHV), feline herpesvirus 1 (FHV), and pseudorabies virus (PRV).

Pharmaceutical Salts

The compound of formula I may be used in its native form or as a salt. In cases where forming a stable nontoxic salt is desired, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, ketoglutarate, and glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, hydrobromide, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a compound of the invention with a suitable acid affording a physiologically acceptable anion.

Routes of Administration

In therapeutic use for treating, or combating, viral infections in a mammal (i.e. human and animals) a compound of the present invention, its pharmaceutical compositions and other antiviral agents can be administered orally, parenterally, topically, rectally, transmucosally, or intestinally.

Parenteral administrations include indirect injections to generate a systemic effect or direct injections to the afflicted area. Examples of parenteral administrations

are subcutaneous, intravenous, intramuscular, intradermal, intrathecal, intraocular, intranasal, intravetricular injections or infusions techniques.

Topical administrations include the treatment of infectious areas or organs readily accessibly by local application, such as, for example, eyes, ears including external and middle ear infections, vaginal, open wound, skins including the surface skin and the underneath dermal structures, or other lower intestinal tract. It also includes transdermal delivery to generate a systemic effect.

The rectal administration includes the form of suppositories.

The transmucosal administration includes nasal aerosol or inhalation applications.

The preferred routes of administration are oral and parenteral.

Composition/Formulation

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, *e.g.*, by means of conventional mixing, dissolving, granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, solutions, emulsions, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. A carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Examples of such carriers or excipients include, but are not limited to, magnesium carbonate, magnesium stearate, talc, sugar, lactose, sucrose, pectin, dextrin, mannitol, sorbitol, starches, gelatin, cellulosic materials, low melting wax, cocoa butter or

powder, polymers such as polyethylene glycols and other pharmaceutical acceptable materials.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, cremophor, capmul, medium or long chain mono-, di- or triglycerides. Stabilizers may be added in these formulations, also.

Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

The compounds may also be formulated for parenteral administration, *e.g.*, by injection, bolus injection or continuous infusion. Formulations for parenteral administration may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

For injection, the compounds of the invention may be formulated in aqueous solution, preferably in physiologically compatible buffers or physiological saline buffer. Suitable buffering agents include trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine.

Parenteral administrations also include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally,

suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

For suppository administration, the compounds may also be formulated by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and other glycerides.

For administration by inhalation, compounds of the present invention can be conveniently delivered through an aerosol spray in the form of solution, dry powder, or suspensions. The aerosol may use a pressurized pack or a nebulizer and a suitable propellant. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler may be formulated containing a power base such as lactose or starch.

For topical applications, the pharmaceutical composition may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion such as suspensions, emulsion, or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, ceteary alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic and otitis uses, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or

preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as a benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be in the form of implants. A compound of this invention may be formulated for this route of administration with suitable polymers, hydrophobic materials, or as a sparing soluble derivative such as, without limitation, a sparingly soluble salt.

Additionally, the compounds may be delivered using a sustained-release system. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for 24 hours or for up to several days.

Dosage

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, the treatment or prevention of infectious diseases. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

The quantity of active component, that is the compound of this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the manner of administration, the potency of the particular compound and the desired concentration. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

Generally, an antiviral effective amount of dosage of active component will be in the range of about 0.1 to about 400 mg/kg of body weight/day, more preferably about 1.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of each subject and the severity of the viral infection being treated.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more

sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired plasma concentration. On the other hand, the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures know in the art may be used to determine the desired dosage amount.

BIOLOGICAL DATA

While many of the compounds of the present invention have shown activity against the CMV polymerase, these compounds may be active against the cytomegalovirus by this or other mechanisms of action. Thus, the description below of these compounds' activity against the CMV polymerase is not meant to limit the present invention to a specific mechanism of action.

The compounds of the present invention have shown activity in one or more of the assays described below. All of these assays are indicative of a compound's activity and thus of its use as an anti-viral agent.

The HCMV polymerase assay is performed using a scintillation proximity assay (SPA) as described in several references, such as N.D. Cook, et al., Pharmaceutical Manufacturing International, pages 49-53 (1992); K. Takeuchi, Laboratory Practice, September issue (1992); US Patent No. 4,568,649 (1986); which are incorporated by reference herein. Reactions are performed in 96-well plates. The assay is conducted in 100 μl volume with 5.4 mM HEPES (pH 7.5), 11.7 mM KCl, 4.5 mM $MgCl_2$, 0.36 mg/ml BSA, and 90 nM ^{3}H-dTTP. Assays are run with and without CHAPS, (3-[(3-Cholamidopropyl)-dimethylammonio]-1-propane-sulfonate) at a final concentration of 2 mM. HCMV polymerase is diluted in enzyme dilution buffer containing 50% glycerol, 250 mM NaCl, 10 mM HEPES (pH 7.5), 100 μg/ml BSA, and 0.01% sodium azide. The HCMV polymerase, which is expressed in recombinant baculovirus-

infected SF-9 cells and purified according to literature procedures, is added at 10% (or 10 μl) of the final reaction volume, i.e., 100 μl. Compounds are diluted in 50% DMSO and 10 μl are added to each well. Control wells contain an equivalent concentration of DMSO. Unless noted otherwise, reactions are initiated via the addition of 6 nM biotinylated poly(dA)-oligo(dT) template/primer to reaction mixtures containing the enzyme, substrate, and compounds of interest. Plates are incubated in a 25 °C or 37 °C H_2O bath and terminated via the addition of 40 μl/reaction of 0.5 M EDTA (pH 8) per well. Reactions are terminated within the time-frame during which substrate incorporation is linear and varied depending upon the enzyme and conditions used, i.e., 30 min. for HCMV polymerase. Ten (10) μl of streptavidin-SPA beads (20 mg/ml in PBS/10% glycerol) are added following termination of the reaction. Plates are incubated 10 min. at 37 °C, then equilibrated to room temperature, and counted on a Packard Topcount. Linear regressions are performed and IC_{50}'s are calculated using computer software.

A modified version of the above HCMV polymerase assay is performed as described above, but with the following changes: Compounds are diluted in 100% DMSO until final dilution into assay buffer. In the previous assay, compounds are diluted in 50% DMSO. 4.5 mM Dithiothreitol (DTT) is added to the polymerase buffer. Also, a different lot of CMV polymerase is used, which appears to be more active resulting in a more rapid polymerase reaction.

Results of the testing of compounds of the present invention in this assay are shown in Tables 1 below.

All results are listed as Polymerase IC_{50} (μM) values. In Table 1, the term "n.d." refers to activity data not determined.

Table 1

Example	Polymerase IC_{50} (μM)		
	HCMV	HSV	VZV
1	0.05	0.20	0.08
2	0.10	0.40	0.20
3	1.77	*nd*	*nd*
4	1.40	*nd*	*nd*
5	2.02	*nd*	*nd*
6	0.06	0.16	0.09
7	0.47	*nd*	*nd*
8	0.62	*nd*	*nd*
9	0.32	*nd*	*nd*
10	0.34	*nd*	*nd*
11	0.10	0.21	0.11
12	0.21	0.62	0.23
13	0.13	0.58	0.20
14	0.62	1.72	*nd*

EXAMPLES

Preparation 1.

_N_-(4-Chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-_b_]-pyridine-5-carboxamide.

Procedure A. _N_-(4-Chlorobenzyl)-2-(hydroxymethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-_b_]pyridine-5-carboxamide (3.00 g, prepared as described in US 6,239,142) is dissolved in DMF (150 mL). DMAP (0.150 g), 2,4,6-collidine (2.73 mL), and methanesulfonyl chloride (1.60 mL) are added, and the reaction mixture is stirred at room temperature for 18 h. The reaction mixture is poured into water (300 mL). The resulting pale yellow solid is filtered off and triturated with acetonitrile to yield 2.75 g of the title compound. Physical characteristics. M.p. 250-256 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48, 8.74, 7.58, 7.41-7.33, 5.16, 4.55, 3.97; ^{13}C NMR (DMSO-d_6) δ 172.5, 164.5, 151.8, 146.4, 138.9, 135.7, 131.7, 130.5, 129.5, 128.7, 124.0, 115.0, 43.4, 41.8, 41.1; MS (EI) _m/z_ 380 (M^+); HRMS (FAB) _m/z_ 381.0255 $(M+H)^+$. Anal. Found: C, 53.34; H, 3.70; N, 7.30; Cl, 17.91; S, 8.51.

Procedure B. A 25 mL round-bottomed flask is charged with _N_-(4-chlorobenzyl)-7-methyl-2-(morpholin-4-ylmethyl)-4-oxo-4,7-dihydrothieno[2,3-_b_]pyridine-5-carboxamide (1.00 g, prepared as described in US 6,239,142) and chloroform (10 ml) via syringe. Ethyl chloroformate (0.55 mL) is added via syringe with stirring under nitrogen. The slurry is heated to reflux overnight. Anhydrous diethyl ether (10 ml) is added to the slurry with stirring under nitrogen. The solid is filtered and washed with diethyl ether (3 x 10 mL). The product is dried in the vacuum oven at 40 °C to afford 0.93 g of the title compound as colorless crystals. Physical characteristics. ^{1}H NMR (400 MHz, TFA-_d_) δ 9.09, 7.69, 7.22, 4.81, 4.62, 4.27; ^{13}C NMR (100 MHz, TFA-_d_) δ 167.6, 166.6, 156.3, 145.2, 143.6, 134.9, 133.3, 129.1, 129.0, 127.4, 119.6, 109.9, 45.2, 44.0, 38.0. Anal. Found: C, 53.44; H, 3.66; N, 7.35; Cl, 18.29.

Preparation 2.

***N*-(4-Chlorobenzyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-(hydroxymethyl)-4-oxo-4,7-dihydr thieno[2,3-*b*]pyridine-5-carboxamide.**

Cesium carbonate (3.91 g) is added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (3.49 g, prepared as described in US 6,239,142) and 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane (1.95 g) in DMF (20 mL). The reaction mixture is stirred at 100 °C for 17 h. The solvent is evaporated and the redisue is dissolved in 10% CH_3OH in CH_2Cl_2. The mixture is washed with water and the organic layer is dried ($MgSO_4$), filtered, and concentrated. The crude product is crystallized from EtOAc to afford 2.7 g of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.70, 7.40, 7.34, 7.28, 5.79, 4.69, 4.53, 4.50, 4.30, 4.14, 3.77, 1.34, 1.23; MS (EI) *m/z* 462 (M^+); HRMS (FAB) *m/z* 463.1087 $(M+H)^+$. Anal. Found: C, 57.07; H, 5.01; N, 6.05.

Preparation 3.

2-(Chloromethyl)-*N*-((4-chlorophenyl)methyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxamide.

2,4,6-Collidine (1.78 mL) and a few crystals of 4-*N*,*N*-dimethylaminopyridine are added to a solution of *N*-(4-chlorobenzyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-(hydroxymethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 2, 2.33 g) in DMF (15 mL). Methanesulfonyl chloride (0.93 mL) is added dropwise and the reaction is stirred at room temperature for 4 hours. The solvent is evaporated and the residue is dissolved in 10% MeOH in CH_2Cl_2. The mixture is washed with water, dried with $MgSO_4$, filtered, and concentrated. The residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2 and the product is crystallized from EtOAc, filtered and washed with ether to afford 1.73 g of the title compound as white crystals. Physical characteristics: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42, 8.73, 7.55, 7.39, 7.34, 5.15, 4.54, 4.51, 4.30, 4.14, 3.77, 1.34, 1.23; HRMS (FAB) *m/z* 481.0758 $(M+H)^+$. Anal. Found: C, 55.18; H, 4.76; N, 5.66.

Preparation 4.

***N*-(4-Chlorobenzyl)-2-(hydroxymethyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

Cesium carbonate (5.54 g) is added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (5.23 g, prepared as described in US 6,239,142) and 2-(3-iodopropoxy)tetrahydro-2*H*-pyran (4.32 g, prepared by mixing equal molar amounts of 2-iodopropanol and 3,4-dihydro-2*H*-pyran) in DMF (20 mL). The mixture is heated at 60 °C for 4 hours. The solvent is evaporated and the residue is dissolved in 10% MeOH in CH_2Cl_2. The mixture is washed with water and the organic layer is dried ($MgSO_4$), filtered, and concentrated. The crude product is purified by chromatographed over silica gel with 5% MeOH in CH_2Cl_2 and recrystallization from EtOAc to afford 4.82 g of the title compound as white crystals. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55, 8.71, 7.39, 7.33, 7.29, 5.79, 4.70, 4.53, 4.49, 4.38, 3.68, 3.37, 2.11, 1.63, 1.53, 1.40; MS (EI) *m/z* 490 (M^+); Anal. Found: C, 58.74; H, 5.66; N, 5.61.

Preparation 5.

***N*-(4-Chlorobenzyl)-2-(chloromethyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)-propyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

2,4,6-Collidine (2.51 mL) and a few crystals of 4-*N*,*N*-dimethylaminopyridine is added to a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 4, 4.0 g) in DMF (20 mL). Methanesulfonyl chloride (1.38 mL) is added dropwise and the reaction is stirred at 60 °C for 5 hours. The solvent is evaporated and the residue dissolved in 10% MeOH in CH_2Cl_2. The mixture is washed with water and the organic layer is dried ($MgSO_4$), filtered, and concentrated. The residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2. The crude product is crystallized from EtOAc, filtered, and washed with ether to afford 2.35 g of the title compound as white crystals. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43, 8.74, 7.56, 7.39, 7.34, 5.15, 4.54, 4.38, 3.70, 3.38, 2.11, 1.61, 1.51, 1.38; MS (EI) *m/z* 508 (M^+); HRMS (FAB) *m/z* 509.1064 $(M+H)^+$. Anal. Found: C, 56.00; H, 5.11; N, 5.56.

Preparation 6.

***N*-(4-Chlorobenzyl)-2-(hydroxymethyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

Cesium carbonate (3.91 g) is added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (3.49 g, prepared as described in US 6,239,142) and 2-(2-iodoethoxy)tetrahydro-2*H*-pyran (2.56 g, prepared by mixing equal molar amounts of 2-iodoethanol and 3,4-dihydro-2*H*-pyran) in DMF (20 mL). The reaction mixture is stirred at 100 °C for 17 hours. The solvent is evaporated and the residue is dissolved in 10% CH_3OH in CH_2Cl_2. The mixture is washed with water and the organic layer is dried ($MgSO_4$), filtered, concentrated. The crude product is crystallized from EtOAc to afford 3.8 g of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59, 8.71, 7.39, 7.38, 7.29, 5.79, 4.69, 4.58, 4.54, 4.48, 3.96, 3.78, 3.30, 1.54, 1.39, 1.29; MS (EI) *m/z* 476 (M^+); HRMS (FAB) *m/z* 477.1245 $(M+H)^+$.

Preparation 7.

***N*-(4-Chlorobenzyl)-2-(chloromethyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)]-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

2,4,6-Collidine (2.9 mL) and a few crystals of 4-*N*,*N*-dimethylaminopyridine is added to a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 6, 3.5 g) in DMF (20 mL). Methanesulfonyl chloride (1.7 mL) is added dropwise and the reaction mixture is stirred at room temperature for 72 h. The reaction mixture is poured into water (100 mL) and filtered. The filtrate is extracted with 10% MeOH in CH_2Cl_2. The organic layer is dried ($MgSO_4$), filtered, and concentrated to afford 2.8 g of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43, 8.75, 7.55, 7.38, 7.33, 5.14, 4.59, 4.53, 4.49, 3.96, 3.79, 3.29, 1.52, 1.38, 1.28; MS (EI) *m/z* 494 (M^+); HRMS (FAB) *m/z* 495.0904 $(M+H)^+$.

Preparation 8.

***N*-(4-Chlorobenzyl)-2-(chloromethyl)-7-(2-hydroxyethyl)]-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide.**

2,4,6-Collidine (2.9 mL) and a few crystals of 4-*N*,*N*-dimethylaminopyridine is added to a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 6, 3.5 g) in DMF (20 mL). Methanesulfonyl chloride (1.7 mL) is added dropwise and the reaction mixture is stirred at room temperature for 72 h. The reaction mixture is poured into water (100 mL) and filtered. The solid is recrystallized from acetonitrile to afford 1.27 g of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47, 8.67, 7.55, 7.40, 7.34, 5.15, 5.14, 4.54, 3.34, 2.51; MS (EI) *m/z* 410 (M^+); HRMS (FAB) *m/z* 411.0332 $(M+H)^+$. Anal. Found: C, 52.27; H, 4.05; N, 6.93.

Preparation 9.

***N*-(4-Chlorobenzyl)-7-ethyl-2-(hydroxymethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide.**

Potassium carbonate (0.87 g) and iodoethane (0.5 mL) are added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (2.0 g, prepared as described in US 6,239,142) in anhydrous DMF (60 mL). The reaction mixture is stirred at room temperature for 18 h. The mixture is diluted with water (150 mL) and filtered. The resulting white powder is washed with water (15 mL) followed by diethyl ether (15 mL) and dried in a vacuum oven to afford 1.64 g of the title compound as a white solid. Physical characteristics. M.p. 169-172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65, 8.74, 7.37, 7.29, 5.81, 4.70, 4.54, 4.32, 1.44; HRMS (FAB) *m/z* 377.0720 $(M+H)^+$. Anal. Found: C, 56.87; H, 4.77; N, 7.38; Cl, 9.35; S, 8.44.

Preparation 10.
***N*-(4-Chlorobenzyl)-2-(chloromethyl)-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide.**

4-*N*,*N*-Dimethylaminopyridine (80 mg), 2,4,6-collidine (1.41 mL), and methanesulfonyl chloride (0.83 mL) are added to a solution of *N*-(4-chlorobenzyl)-7-ethyl-2-(hydroxymethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 9, 1.61 g) in anhydrous DMF (80 mL). The reaction mixture is stirred at room temperature for 24 h. The mixture is diluted with water (150 mL) and filtered. The resulting white powder is recrystallized from acetonitrile and dried in a vacuum oven to afford 1.4 g of the title compound as a white solid. Physical characteristics. M.p. 199-200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.45, 8.77, 7.57, 7.38, 5.15, 4.54, 4.32, 1.44. Anal. Found: C, 54.53; H, 3.94; N, 7.03; Cl, 17.57; S, 8.09.

Preparation 11.
***N*-(4-Chlorobenzyl)-7-propyl-2-(hydroxymethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide.**

Potassium carbonate (0.91 g) and 1-iodopropane (0.64 mL) are added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (2.0 g, prepared as described in US 6,239,142) in anhydrous DMF (60 mL). The reaction mixture is stirred at room temperature for 4 h. The mixture is diluted with water (150 mL) and filtered. The resulting white powder is washed with water (15 mL) followed by diethyl ether (15 mL) and dried in a vacuum oven to afford 1.73 g of the title compound as a white solid. Physical characteristics. M.p. 174-175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62, 8.72, 7.38, 7.29, 5.80, 4.69, 4.55, 4.27, 1.87, 0.89; Anal. Found: C, 58.20; H, 4.96; N, 7.13; Cl, 8.98; S, 8.16.

Preparation 12.

***N*-(4-Chlorobenzyl)-2-(chloromethyl)-7-propyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide.**

4-*N*,*N*-Dimethylaminopyridine (80 mg), 2,4,6-collidine (1.39 mL), and methanesulfonyl chloride (0.81 mL) are added to a solution of *N*-(4-chlorobenzyl)-7-propyl-2-(hydroxymethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 11, 1.63 g) in anhydrous DMF (80 mL). The reaction mixture is stirred at room temperature for 24 h. The mixture is diluted with water (150 mL) and filtered. The resulting light yellow powder is recrystallized from acetonitrile and dried in a vacuum oven to afford 1.4 g of the title compound as a light yellow solid. Physical characteristics. M.p. 186.5-188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.45, 8.75, 7.56, 7.39, 5.15, 4.54, 4.27, 1.85, 0.91. Anal. Found: C, 55.76; H, 4.59; N, 6.95; Cl, 16.88; S, 7.80.

Preparation 13.

***N*-(4-Chlorobenzyl)-2-(hydroxymethyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide.**

Potassium carbonate (5.0 g) and bromoethylmethyl ether (5.0 g) are added to a solution of *N*-(4-chlorobenzyl)-4-hydroxy-2-(hydroxymethyl)thieno[2,3-*b*]pyridine-5-carboxamide (11.4 g, prepared as described in US 6,239,142) in anhydrous DMF (350 mL). The reaction mixture is stirred at room temperature for 18 h. The mixture is diluted with water (600 mL) and filtered. The resulting white powder is dried in a vacuum oven to afford 8.44 g of the title compound as a white solid. Physical characteristics. M.p. 193 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58, 8.65, 7.37, 7.29, 5.82, 4.70, 4.54, 4.47, 3.76, 3.24; HRMS (FAB) *m/z* 407.0836 $(M+H)^+$. Anal. Found: C, 55.81; H, 4.71; N, 6.90; Cl, 8.58; S, 7.81.

Preparation 14.

***N*-(4-Chlorobenzyl)-2-(chloromethyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide.**

4-*N*,*N*-Dimethylaminopyridine (360 mg), 2,4,6-collidine (6.5 mL), and methanesulfonyl chloride (3.8 mL) are added to a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 13, 8.0 g) in anhydrous DMF (360 mL). The reaction mixture is stirred at room temperature for 18 h. The mixture is diluted with water (600 mL) and filtered. The resulting off-white powder is dried in a vacuum oven to afford 7.03 g of the title compound as an off-white solid. Physical characteristics. M.p. 192-193 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48, 8.67, 7.55, 7.37, 5.14, 4.53, 4.46, 3.74, 3.24; HRMS (FAB) *m/z* 425.0480 $(M+H)^+$. Anal. Found: C, 53.38; H, 4.37; N, 6.66; Cl, 15.77; S, 7.69.

Preparation 15.

***rac*-1-(3-Methoxyphenyl)-2-(methylamino)ethanol.**

A mixture of (3-methoxyphenyl)oxirane (Perrone, R. *J. Med. Chem.*, *35*, **1992**, 3045-3049) (3.00 g) and a solution of methylamine (2.0 M in methanol, 20 mL) is heated in a sealed tube at 100 °C for 4 h. After cooling, the solvent is evaporated under reduced pressure and the residue is purified by column chromatography (CH_2Cl_2 / CH_3OH / triethylamine, 90/9/1) to yield 1.16 g of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22, 6.93, 6.90, 6.78, 4.72, 3.77, 2.67, 2.34; MS (ESI-) *m/z* 272 $(M-H)^-$.

Preparation 16.

***rac*-4-(1-Hydroxy-2-(methylamino)ethyl)benzonitrile.**

A mixture of 4-oxiran-2-ylbenzonitrile (Nobuya, T. *Chem. Pharm. Bull.*, **1982**, *30*, 1393-1400) and a solution of methylamine (2.0 M in methanol, 10 mL) is heated in a sealed tube at 100 °C for 4 h. After cooling, the solvent is evaporated under reduced pressure and the residue is chromatographed with CH_2Cl_2 / CH_3OH / triethylamine

(90/9/1) to obtain 0.94 g of the title compound as an off-white solid. Physical characteristics. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63, 7.49, 4.84, 2.87, 2.68, 2.49. MS (ESI+) *m/z* 177 (M+H).

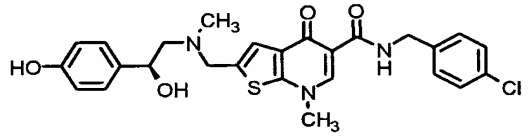
Preparation 17.

***rac*-3-(1-Hydroxy-2-(methylamino)ethyl)benzonitrile.**

A mixture of 3-oxiran-2-ylbenzonitrile (Barrow, J. *Biorg. Med. Chem. Lett.*, **2001**, *11*, 2691-2696) (1.46 g) and a solution of methylamine (2.0 M in methanol, 10 mL) is heated in a sealed tube at 100 °C for 4 h. After cooling, the solvent is evaporated under reduced pressure and the residue is chromatographed with CH_2Cl_2 / CH_3OH / triethylamine (90/9/1) to obtain 0.73 g of the title compound as an off-white solid. Physical characteristics. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69, 7.61, 7.56, 7.45, 4.81, 2.82, 2.67, 2.46; MS (ESI+) *m/z* 177 (M+H).

Example 1.

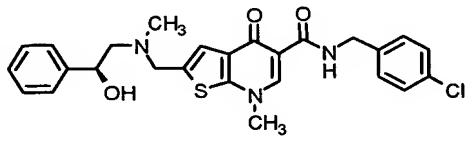
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-hydroxyphenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide .**



rac-N-(4-Chlorobenzyl)-2-(((2-hydroxy-2-(4-hydroxyphenyl)ethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (US patent 6,239,142) is resolved preparatively on a 5 x 50 cm Chiralcel OJ column. The mobile phase is 100% absolute ethanol with a flow rate of 75 mL/min. Peaks are detected by UV at 215 nm. A 110 mg sample is injected. The more quickly eluting enantiomer is isolated and then further purified by recrystallization from ethyl acetate/acetonitrile to yield 0.049 g of the title compound as an off-white solid. Physical characteristics. M.p. 134-143 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60, 9.25, 8.69, 7.41-7.29, 7.12-7.09, 6.70-6.67, 4.95, 4.68-4.60, 4.55, 3.92, 3.83, 2.65-2.55, 2.30; $[\alpha]^{25}_D$ = +18 (*c* 0.62, methanol); Anal. Found: C, 60.47; H, 5.37; N, 8.00.

Example 2.

***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide .**



4-*N*,*N*-Dimethylaminopyridine (16 mg), 2,4,6-collidine (0.27 mL), and methanesulfonyl chloride (0.16 mL) are added to a solution of *N*-(4-chlorobenzyl)-2-(hydroxymethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (0.300 g) (US patent 6,239,142) in DMF (17 mL). The reaction mixture is stirred at room temperature for 1 h. (1*S*)-2-(Methylamino)-1-phenylethanol (Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *J. Chem. Soc. Perkin Trans.* I, **1989**, 2223-2228) (1.26 g) is dissolved in DMF (5 mL) and added. The reaction mixture is stirred at room temperature for 18 h. The reaction mixture is poured into water (50 mL). The resulting off-white solid is purified by column chromatography (CH_2Cl_2/methanol; 99/1, 95/5). The resulting yellow solid is recrystallized twice from acetonitrile to yield 0.056 g of the title compound as a white solid. Physical characteristics. M.p. 162-164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61, 8.69, 7.41-7.39, 7.38-7.25, 7.24-7.21, 5.17, 4.78-4.74, 4.55, 3.91, 3.86, 2.68-2.63, 2.58-2.54, 2.31; MS (ESI+) *m/z* 496 $(M+H)^+$; HRMS (FAB) *m/z* 496.1460 $(M+H)^+$; $[\alpha]^{25}_D = +4$ (*c* 0.48, DMSO); Anal. Found: C, 61.15; H, 5.53; N, 8.27; Cl, 6.21; S, 5.67.

Preparation 18.

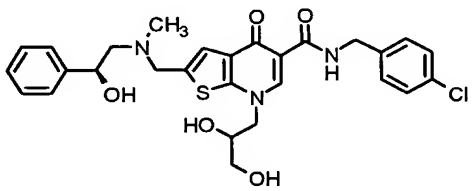
***N*-(4-Chlorobenzyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

Cesium carbonate (230 mg) and 3Å Sieves (100 mg) are added to a solution of 2-(chloromethyl)-*N*-((4-chlorophenyl)methyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)-methyl]-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 3, 241 mg) and (1*S*)-2-(methylamino)-1-phenylethanol (130 mg) in DMF (2.0 mL). The reaction mixture is placed on a shaker block at 60 °C for 17 h. The solvent is then

evaporate and the residue is purified by chromatography over silica gel with 5% MeOH in CH_2Cl_2 to afford 115 mg of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.67, 7.40-7.22, 5.12, 4.75, 4.53, 4.45, 4.28, 4.14, 3.82, 3.77, 2.73, 2.58, 2.31, 1.33, 1.23; HRMS (FAB) *m/z* 546.1463 $(M+H)^+$.

Example 3.

***N*-(4-Chlorobenzyl)-7-(2,3-dihydroxypropyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)-(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



N-(4-Chlorobenzyl)-7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 18, 100 mg) is dissolved in THF (10 mL) and 65 % Perchloric acid (0.2 mL) is added. The reaction is stirred for 6 hours at ambient temperature, then poured into sat. $NaHCO_3$ solution, extracted with EtOAc (100 mL) dried with $MgSO_4$, filtered and concentrated. The residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2 to give 56 mg of a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.60, 7.40, 7.35-7.28, 7.22, 5.30, 5.14, 4.98, 4.75, 4.53, 4.29, 4.11, 3.50, 3.36, 2.63, 2.51, 2.31; HRMS (FAB) *m/z* 556.1683 $(M+H)^+$.

Preparation 19.

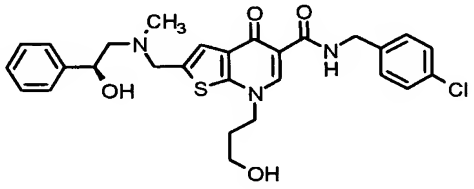
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino]methyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide.**

Cesium carbonate (260 mg) and 3Å Sieves (100 mg) are added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 5, 225 mg) and (1*S*)-2-

(methylamino)-1-phenylethanol (121 mg) in DMF (3.0 mL). The reaction mixture is placed on a shaker block at 60 °C for 17 h. The solvent is evaporatedand the residue is purified by chromatography over silica gel with 5% MeOH in CH_2Cl_2 to afford 154 mg of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.67, 7.40-7.24, 7.22, 5.14, 4.76, 4.53, 4.48, 4.33, 3.84, 3.69, 3.36. 2.66, 2.56, 2.09, 1.62, 1.54, 1.09; HRMS (FAB) *m/z* 624.2313 $(M+H)^+$.

Example 4.

***N*-(4-chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-(3-hydroxypropyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



N-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino]methyl)-4-oxo-7-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 19, 85 mg) is dissolved in THF (10 mL) and 65 % perchloric acid (0.2 mL) is added. The reaction mixture is stirred for 4 h at room temperature and is then poured into sat. $NaHCO_3$ solution. The mixture is extracted with EtOAc (100 mL) and the organic layer is dried ($MgSO_4$)„ filtered, and concentrated. The residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2 to afford 100 mg of the title compound as an oil. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.67, 7.41, 7.38-7.30, 7.23, 5.16, 4.77, 4.53, 4.30, 3.84, 3.47, 2.63, 2.59, 1.97; HRMS (FAB) *m/z* 540.1710.

Preparation 20.

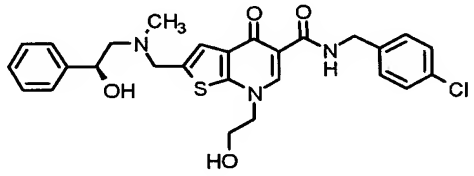
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

Cesium carbonate (260 mg) and 3Å Sieves (100 mg) are added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl))-4,7-

dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 7, 300 mg) and (1*S*)-2-(methylamino)-1-phenylethanol (113 mg) in DMF (3.0 mL). The reaction mixture is placed on a shaker block at 60 °C for 17 h. The solvent is evaporated and the residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2 to afford 121 mg of the title compound as a white solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54, 8.71, 7.38, 7.34-7.28, 7.23, 5.14, 4.75, 4.58, 4.54, 4.44, 3.95, 3.84, 3.78, 3.30, 2.63, 2.59, 2.31, 1.53, 1.38, 1.27; HRMS (FAB) *m/z* 610.2164 $(M+H)^+$.

Example 5.

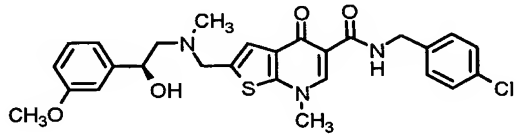
***N*-(4-Chlorobenzyl)-7-(2-hydroxyethyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)-(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



N-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 20, 56 mg) is dissolved in THF (3 mL) and 65 % perchloric acid (0.2 mL) followed by water (0.2 mL) are added. The reaction mixture is stirred at room temperature for 2 h and is then poured into sat. $NaHCO_3$ solution. The mixture is extracted with EtOAc (150 mL) and the organic layer is dried ($MgSO_4$), filtered, and concentrated. The residue is chromatographed over silica gel with 5% MeOH in CH_2Cl_2 and the crude product is crystallized from EtOAc/ether to afford 26 mg of the title compound as white crystals. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53, 8.62, 7.39, 7.32, 7.24, 5.16, 4.78, 4.53, 4.27, 3.82, 3.79, 2.62, 2.58, 2.31; HRMS (FAB) m/z 526.1567 $(M+H)^+$.

Example 6.

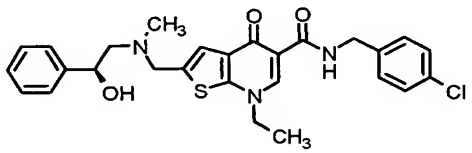
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(3-methoxyphenyl)ethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



rac-1-(3-Methoxyphenyl)-2-(methylamino)ethanol (Preparation 15, 66 mg) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxamide (Preparation 1, 100 mg) and *N*,*N*-diisopropyl-ethylamine (63 μL) in dry DMF (5 mL). The reaction mixture is stirred for 18 h at room temperature. The mixture is poured into of CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL). The organic layer is dried (Na_2SO_4), filtered, and the solvent is evaporated. The crude solid is chromatographed with MeOH/CH_2Cl_2 (1-5% gradient) to obtain 90 mg of a pale yellow solid. The racemate is resolved preparatively on a Chiralcel OJ column eluting with 0.1% diethylamine/EtOH. The slower eluting enantiomer is isolated to afford the title compound. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62, 8.69, 7.41-7.31, 7.22, 6.90, 6.89, 6.78, 5.15, 4.73, 4.54, 3.92, 3.84, 3.71, 2.61, 2.31; MS (ESI+) *m/z* 526 $(M+H)^+$; HRMS (FAB) *m/z* 526.1555 $(M+H)^+$; $[\alpha]^{25}_D$ = +5 (*c* 0.95, DMSO).

Example 7.

***N*-(4-Chlorobenzyl)-7-ethyl-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)-methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide. .**

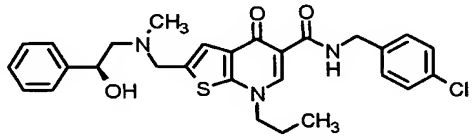


N,*N*-Diisopropylethylamine (220 μL) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-ethyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 9, 250 mg) and (1*S*)-2-(methylamino)-1-phenylethanol (208 mg) in DMF (14 mL). The reaction mixture is stirred at 90 °C for 4 h and cooled to room temperature. The mixture is diluted with water (30 mL) and filtered. The resulting

off-white powder is recrystallized from acetonitrile to afford 73 mg of the title compound as a white solid. Physical characteristics. M.p. 100-102 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60, 8.72, 7.32, 5.16, 4.77, 4.54, 4.26, 3.84, 2.62, 2.32, 1.42; HRMS (FAB) *m/z* 510.1625 $(M+H)^+$.

Example 8.

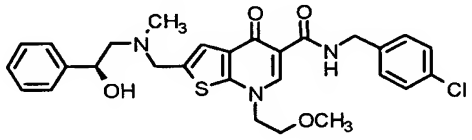
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-4-oxo-7-propyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



N,*N*-Diisopropylethylamine (213 μL) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-propyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 10, 250 mg) and (1*S*)-2-(methylamino)-1-phenylethanol (202 mg) in DMF (14 mL). The reaction mixture is stirred at 90 °C for 4 h and cooled to room temperature. The mixture is concentrated in vacuo to a yellow oil. The crude product is chromatographed, eluting with 1% MeOH/$CHCl_3$, to afford 205 mg of the title compound as a white foaming solid. Physical characteristics. M.p. 45-48 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63, 8.70, 7.35, 5.17, 4.54, 4.21, 3.83, 2.62, 2.32, 1.84, 0.91; HRMS (FAB) *m/z* 524.1766 $(M+H)^+$.

Example 9.

***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-phenylethyl)(methyl)amino)methyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

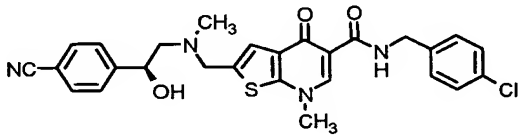


N,*N*-Diisopropylethylamine (404 μL) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 11, 500 mg) and (1*S*)-2-(methylamino)-1-phenylethanol (390 mg) in DMF (24 mL). The reaction mixture is stirred at 90 °C for 4 h and cooled

to room temperature. The mixture is concentrated in vacuo to a yellow oil and triturated with diethyl ether to afford 172 mg of the title compound as an off-white solid. Physical characteristics. M.p. 105-106 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58, 8.63, 7.32, 5.16, 4.75, 4.54, 4.42, 3.85, 3.73, 3.25, 2.60, 2.32. HRMS (FAB) *m/z* 540.1723 $(M+H)^+$; $[\alpha]^{25}_D$ = +43 (*c* 0.9, CH_2Cl_2). Anal. Found: C, 61.95; H, 5.51; N, 7.65; Cl, 6.58; S, 5.97.

Example 10.

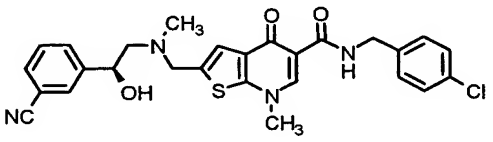
***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-cyanophenyl)ethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



rac-4-(1-Hydroxy-2-(methylamino)ethyl)benzonitrile (Preparation 16, 141 mg) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 1, 200 mg) and *N*,*N*-diisopropylethylamine (0.18 mL) in dry DMF (7 mL). The reaction mixture is stirred for 18 h at room temperature. The mixture is poured into of CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL). The organic layer is dried (Na_2SO_4), filtered, and the solvent is evaporated. The crude solid is chromatographed with MeOH/CH_2Cl_2 (1-5% gradient) to obtain 268 mg of a white solid. The racemate is resolved preparatively on a Chiralcel OJ column eluting with 0.1% diethylamine/EtOH. The faster eluting enantiomer is isolated to afford the title compound. Physical characteristics. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56, 8.62, 7.62, 7.47, 7.44, 7.30-7.26, 4.90, 4.61, 4.02, 3.90, 2.68, 2.48; HRMS (FAB) *m/z* 521.1414 $(M+H)^+$; $[\alpha]^{25}_D$ = +11 (c 0.66, DMSO).

Example 11.

***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(3-cyanophenyl)ethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



rac-3-(1-Hydroxy-2-(methylamino)ethyl)benzonitrile (Preparation 17, 141 mg) is added to a solution of *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 1, 200 mg) and *N*,*N*-diisopropylethylamine (0.18 mL) in dry DMF (7 mL). The reaction mixture is stirred for 18 h at room temperature. The mixture is poured into of CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL). The organic layer is dried (Na_2SO_4), filtered, and the solvent is evaporated. The crude solid is chromatographed with MeOH/CH_2Cl_2 (1-5% gradient) to obtain 210 mg of a white solid. The racemate is resolved preparatively on a Chiralcel OJ column eluting with 0.1% diethylamine/EtOH. The faster eluting enantiomer is isolated to afford the title compound. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57, 8.69, 7.77, 7.73, 7.69, 7.54, 7.39, 7.33, 7.29, 5.47, 4.82, 4.54, 3.91, 3.80, 2.64, 2.30; HRMS (FAB) *m/z* 521.1422 $(M+H)^+$; $[\alpha]^{25}_D = +11$ (DMSO).

Preparation 21.

***N*-(4-Chlorobenzyl)-7-methyl-2-((methylamino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**

N-(4-Chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 1, 2.00 g) is suspended in DMF (120 mL), and a 2.0 *M* solution of methylamine in THF (27 mL) is added. The reaction mixture is heated to 70 °C for 1 h. The reaction is allowed to cool to room temperature and is poured into water (350 mL). The resulting solid is filtered and purified by column chromatography (CH_2Cl_2/methanol; 98/2, 95/5) to yield 1.07 g of the title compound as a white solid. Physical characteristics. M.p. 196-199 °C; ^{1}H NMR (400 MHz,

DMSO-d_6) δ 10.62, 8.69, 7.41-7.31, 4.55, 3.95, 3.88, 2.30; MS (ESI+) *m/z* 376 $(M+H)^+$; Anal. Found: C, 57.30; H, 4.86; N, 11.06; Cl, 9.23; S, 8.28.

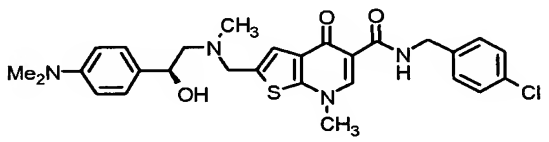
Preparation 22.

5 *N*-(4-Chlorobenzyl)-2-(((2-(4-(dimethylamino)phenyl)-2-oxoethyl)(methyl)-amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.

A mixture of 2-bromo-1-(4-(dimethylamino)phenyl)ethanone (0.28 g), anhydrous potassium carbonate (0.076 g), and *N*-(4-chlorobenzyl)-7-methyl-2-((methylamino)-
10 methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 21, 0.20 g) in dry DMF (5 mL) is stirred for 24 h at room temperature and the the solvent is evaporated at 30°/1 mm. The residue is washed with water (20 mL) and purified by column chromatography (chloroform/methanol, 98/2) to afford 0.186 g of the title compound as a pale yellow solid. Physical characteristics. M.p. 162 °C. Anal. Found:
15 C, 62.61; H, 5.59; N, 10.35.

Example 12.

20 *N*-(4-Chlorobenzyl)-2-((((2*S*)-2-(4-(dimethylamino)phenyl)-2-hydroxyethyl)-(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.



25 *N*-(4-Chlorobenzyl)-2-(((2-(4-(dimethylamino)phenyl)-2-oxoethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 22, 0.50 g) is dissolved in a mixture of methanol (10 mL), THF (2.5 mL), and chloroform (2.5 mL). Sodium borohydride (0.10 g) is added and the mixture is stirred for 1 h. The mixture is cooled to –10 °C and the solid filtered. The crude product is
30 recrystallized from CH_2Cl_2/methanol to afford 0.107 g of racemic compound. The racemate (326 mg) is resolved preparatively on a Chiralcel OD column (5 x 50 cm) using recycling LC eluting with absolute ethanol containing 0.1% DEA. The slower eluting enantiomer is isolated and further purified by column chromatography

(chloroform/methanol, 99/1 – 97/3) to afford 71 mg the title compound as a white solid. Physical characteristics. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62, 8.69, 7.40, 7.34, 7.30, 7.13, 6.67, 4.87, 4.63, 4.54, 3.92, 3.83, 2.85, 2.30.

Preparation 23.

***tert*-Butyl 2-(4-Bromophenyl)-2-oxoethyl(methyl)carbamate.**

2,4′-Dibromoacetophenone (2.78 g) is dissolved in dry THF (20 mL) under nitrogen and cooled in ice. A 2M solution of methylamine in THF (10 mL) is added rapidly and the reaction stirred for 2 h. The resulting suspension is filtered and the filtrate treated with di-*tert*-butyl carbonate (2.18 g) at 0 °C. After 1 h, the solvent is evaporated and the residue is purified by column chromatography (hexane/EtOAc, 9/1) to afford 1.83 g of the title compound as a pale orange solid. Physical characteristics. M.p. 87-90 °C. Anal. Found: C, 51.18; H, 5.54; N, 4.24.

Preparation 24.

***tert*-Butyl 2-(4-Bromophenyl)-2-hydroxyethyl(methyl)carbamate.**

Sodium borohydride (0.189g) is added to a solution of *tert*-butyl 2-(4-bromophenyl)-2-oxoethyl(methyl)carbamate (Preparation 23, 1.39 g) in a mixture of dry THF (25 mL) and ethanol (5 mL). The reaction mixture is stirred for 1 h, and the solvent is evaporated. The residue is purified by column chromatography (chloroform/methanol, 95/1) to afforded 1.33 g of the title compound as a pale yellow solid. Physical characteristics. M.p. 80-82 °C. Anal. Found: C, 50.91; H, 6.09; N, 4.27.

Preparation 25.

***tert*-Butyl 2-(4-Formylphenyl)-2-hydroxyethyl(methyl)carbamate.**

tert-Butyl 2-(4-bromophenyl)-2-hydroxyethyl(methyl)carbamate (Preparation 24, 0.25 g) is dissolved in dry THF (5ml) under nitrogen and the solution is cooled to 0 °C. Tetramethylethylenediamine (0.22 g) is added followed by a 3 M solution of MeMgBr in ether (0.30 mL). After 30 min, the reaction mixture is cooled to –35 °C and a 1.6 M solution of *n*-butyl lithium in hexane (2.0 mL) is added. After 2 h, dry DMF (0.284 g)

is added and the mixture is stirred overnight. A saturated solution of ammonium chloride (1.5 mL) is added followed by water (15 mL). The mixture is extracted with EtOAc (2 x 50 mL). The combined organic layer is concentrated and the crude product is purified by column chromatography (hexane/EtOAc, 3/1) to afford 0.294 g of the title compound as a pale yellow gum which crystallized on standing to afford a waxy white solid. Physical characteristics. M.p. 37-39 °C.

Preparation 26

***tert*-Butyl 2-Hydroxy-2-(4-(hydroxymethyl)phenyl)ethyl(methyl)carbamate.**

Sodium borohydride (0.25 g) is added to a solution of *tert*-butyl 2-(4-formylphenyl)-2-hydroxyethyl(methyl)carbamate (Preparation 25, 1.808 g) in a mixture of dry THF (50 mL) and ethanol (10 mL) cooled in an ice bath. The reaction mixture is stirred for 1 h and then the solvent is evaporated. The residue is partitioned between sat. aqueous ammonium chloride solution (50 mL) and chloroform (50 mL), and the aqueous layer is further extracted with chloroform (2 x 50 mL). The combined organic layers are concentrated to afford 1.82 g of the title compound as an off white gum. Physical characteristics. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49, 2.83, 3.33-3.47, 3.54, 4.72, 4.96, 7.38; HRMS (FAB) *m/z* 282.1707 $(M+H)^+$.

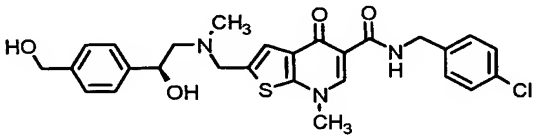
Preparation 27.

1-(4-(Hydroxymethyl)phenyl)-2-(methylamino)ethanol.

A mixture of *tert*-butyl 2-hydroxy-2-(4-(hydroxymethyl)phenyl)ethyl(methyl)carbamate (Preparation 26, 1.804g) and a 4 M HCl solution in dioxane (10 mL) is stirred for 3 h. The solvent is evaporated and the residue is dissolved in methanol (35 mL). The solution is stirred with a resin of MP-carbonate (3 g) for 4 days. Filtration followed by purification by column chromatography (chloroform/methanol, 85/15 containing 1.5 % conc. ammonia) to afford 0.462 g of the title compound as white crystals. Physical characteristics. M.p. 80-81 °C. Anal. Found: C, 66.05; H, 8.37; N, 7.66.

Example 13.

***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-(hydroxymethyl)phenyl)ethyl)-(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



1-(4-(Hydroxymethyl)phenyl)-2-(methylamino)ethanol (Preparation 27, 0.185 g) is shaken in dry DMF (7 mL) for 3 h with 3A molecular sieves (1.3 g). *N*-(4-Chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide (Preparation 1, 0.286 g) and diisopropylethylamine (190 μL) are added and the mixture is shaken for 4 days. The mixture is filtered and the filtrate concentrated (40 °C, 1 mm). The residue is purified by column chromatography (chloroform/methanol, 97/3) to afford 0.294 g of the racemic compound. The racemate (169 mg) is resolved preparatively on a Chiralpak AD column (5 x 25 cm) eluting with methanol containing 0.1% DEA. The faster eluting enantiomer is isolated and further purified by column chromatography (chloroform/methanol, 98/1 – 97/3) to afford 59 mg of the title compound as a white solid. Physical characteristics. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60, 8.70, 7.32, 5.12, 4.75, 4.54, 4.47, 3.92, 3.82, 2.60, 2.31.

Preparation 28.

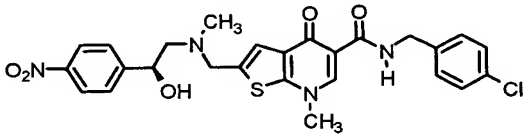
***rac*-2-(Methylamino)-1-(4-nitrophenyl)ethanol.**

Sodium borohydride (0.27 g) is added to methanol (10 mL), stirred 30 min and added is added dropwise to a solution of 2-bromo-4′-nitroacetophenone (3.5 g) in methanol (10 mL) at 0 °C. The solution is stirred 30 min and 1 N HCl is added dropwise until the solution is neutral. The organic layer is separated, washed with brine, dried ($MgSO_4$), filtered and concentrated to provide 3.34 g of a yellow crystalline solid. The crude 2-bromo-1-(4-nitrophenyl)ethanol is dissolved in methanol (20 mL), cooled to 0 °C and sodium methoxide (0.81 g) is added. After 10 min, the ice bath is removed and the reaction mixture is allowed to warm to room temperature. After 30 min, the

reaction mixture is concentrated and extracted with CH_2Cl_2. The organic layers are washed with $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated to afford 1.86 g of a pale yellow solid. A solution of the resulting 2-(4-nitrophenyl)oxirane (0.86 g) in methanol (5 mL) is added dropwise to a solution of methylamine in methanol (2 M, 12 mL) and is stirred vigorously in a sealed tube. After 2.5 h the reaction is concentrated to provide 0.81 g of the title compound as a pale yellow crystalline solid. Physical characteristics. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21-8.19, 7.64-7.62, 4.83-4.80, 2.72-2.63, 2.33; HRMS (ES) *m/z* 197.0932 $(M+H)^+$.

Example 14.

***N*-(4-Chlorobenzyl)-2-((((2*S*)-2-hydroxy-2-(4-nitrophenyl)ethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide.**



A mixture of *rac*-2-(methylamino)-1-(4-nitrophenyl)ethanol (Preparation 28, 0.232 g), *N*-(4-chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide (Preparation 1, 0.300 g) and diisopropylethylamine (0.25 mL) in *N*,*N*-dimethylformamide (10 mL) is heated at 80°C for 3 h. Saturated $NaHCO_3$ solution is added and the mixture extracted with CH_2Cl_2. The combined organic layers are dried ($MgSO_4$), filtered and concentrated. The product is purifed with chromatotron (2 mm silica, CH_2Cl_2/methanol, 98/2; 90/10) to obtain 0.290 g, of the racemic compound. The racemate is resolved preparatively on a 0.46 x 25 cm Chiralpak AD column (Chiral Technologies), at a column temperature of 30 °C. The mobile phase is ethanol/0.1% diethylamine with a flow rate of 0.5 mL/min. Peaks are detected by UV at 230 nm. The faster eluting enantiomer had a retention time of 102.1, while the slower eluted at 119.4. The enantiomers are independently further purified by chromatotron (CH_2Cl_2/methanol, 90/10). The slower eluting isomer is isolated to afford the title compound. Physical characteristics. M.p. 181-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61, 8.68, 8.21-8.19, 7.62-7.60, 7.41-7.39, 7.35-7.33, 5.57-5.56, 4.94-4.91, 4.55-4.53, 3.87, 3.87-3.77, 2.72-2.61, 2.33; HRMS (ES) *m/z* 541.1317 $(M+H)^+$.